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# PSYCHOPHARMACOLOGICAL TECHNIQUES FOR OPTIMIZING HUMAN PERFORMANCE

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PSYCHOPHARMACOLOGICAL TECHNIQUES FOR OPTIMIZING HUMAN PERFORMANCE

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## SUMMARY

Military missions may impose altered work-rest schedules, require sustained performance, and demand work under conditions of sleep loss. In operational environments, administration of psychopharmacological agents could be employed to optimize and maintain performance. Selection of pharmacological agents for military use requires detailed knowledge of the effective dose range, behavioral time course of action, and withdrawal and/or side effects. In order to provide such data, research in "behavioral psychopharmacology" must be a priority in military laboratories.

One technique of considerable military importance is use of sleeping aids to promote rapid sleep onset and permit efficient utilization of rest periods. Over the past four years, behavioral psychopharmacological research at the Naval Health Research Center (NHRC) has emphasized laboratory evaluation of sleeping aids for operational use. The methodology devised to date in this research program is more generally applicable to the evaluation of all psychoactive drugs, including stimulants, and is potentially useful for testing the effects of toxic agents and/or antidotes.

To be suitable for use in operational settings, a sleeping aid must meet specific criteria: 1) It must be effective over the period of intended administration in reducing sleep latency and increasing sleep efficiency; 2) Adverse effects on performance must be absent or limited to a well-defined time period post-administration; drug-induced alterations in arousability from sleep (such as elevation of auditory arousal threshold) or in memory functions (such as anterograde or retrograde amnesias) must be identified; 3) Development of tolerance and occurrence of withdrawal effects and side effects should be rare or nonexistent. The laboratory method for evaluation of sleeping aids is described in this paper.

Our laboratory research has focused on two potentially suitable sleeping aids, the triazolobenzodiazepine triazolam (Halcion®) and the dietary amino acid, L-tryptophan. Triazolam was of potential military interest because its short half-life, reported to be within the range of 2-3 hours, suggested that this drug might promote improved nighttime sleep without producing daytime performance impairment. In earlier studies, triazolam was demonstrated to be an effective hypnotic in doses ranging from 0.25-1.0 mg. There had been several previous studies which assessed morning performance following bedtime triazolam administration. The results of these studies differed, depending upon the dose size, schedule of performance testing, and type of performance task used. L-tryptophan, the amino acid, was studied because of previous reports of its more "natural" hypnotic effects. In our initial evaluation of daytime hypnotic effects, L-tryptophan 4 g reduced nap sleep latency by 46%. Its efficacy in daytime administration suggested its possible operational use in alleviating sleep problems due to jet lag or altered work-rest schedules. There had been little previous research on the effects

of tryptophan on performance.

In laboratory study of triazolam 0.5 mg, sleep latency was reduced and morning performance was unimpaired, although a clear performance decrement was present up to 5 hours post-administration. Triazolam also produced anterograde amnesia--that is, impairment of recall for stimuli presented during the effective phase of drug action--and elevated auditory threshold for arousal from sleep. This alteration of the sleeper's responsivity to auditory stimuli would act to maintain sleep in noisy environments, but it might also render the sleeper impervious to important auditory signals used in an operational environment. In operational use, triazolam could be effectively administered when rest periods of 8 hours duration are scheduled. However, based on our data, personnel would be more difficult to arouse from sleep, would perform less effectively when awakened, and would have mnemonic impairment up to 5 hours post-administration of triazolam.

In nighttime administration to chronic poor sleepers, l-tryptophan 3 g reduced sleep latency after three nights of administration and had no adverse performance effects. The absence of performance effects is an important factor in the potential usefulness of l-tryptophan to the military. However, the late appearance of the hypnotics effects will require further evaluation. In our earlier study assessing daytime hypnotic effectiveness in "good" and "average" sleepers, substantial sleep-inducing effects were present on the first day of administration. In the twelve night study, chronic "poor" sleepers were specifically chosen as subjects to provide a rigorous test of l-tryptophan's hypnotic effectiveness. The late hypnotic effects are probably a reflection of the difference between the daytime and nighttime studies in the type of subject recruited for participation.

The suitability of both triazolam and l-tryptophan for military use will be further evaluated in field research and tested in operational environments. Another psychopharmacological approach to be considered is administration of carefully-chosen stimulants to maintain alertness and performance effectiveness when there is no opportunity for sleep. The techniques developed in this on-going research program in behavioral psychopharmacology will be employed to evaluate stimulants for operational use.

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## 1. BACKGROUND

Military missions may impose altered work-rest schedules, require sustained performance, and demand work under conditions of sleep loss, all of which can result in degradation of human effectiveness. In operational settings, carefully selected psychoactive agents could be administered to optimize and maintain performance effectiveness. The development of successful psychopharmacological strategies to enhance human performance is dependent upon the availability of adequate and reliable information about the drug, or drugs, to be employed. Therapeutic guidelines, as found in such sources as the Physicians' Desk Reference [1] or in Goodman and Gilman [2], are not adequately detailed nor operationally relevant to be useful in planning pharmacological strategy. Because of the unique nature of military missions and operational environments, psychopharmacological research techniques must be employed in the selection of appropriate agents for operational use. Factors such as effective dose range, behavioral time course of action, and withdrawal effects must be clearly delineated. Therefore, research in "behavioral psychopharmacology" must be a priority in military laboratories. Within this approach, a three-stage evaluative process may be employed to evaluate psychopharmacological agents for military use: (1) laboratory research, primarily intended to assess efficacy in target populations and obtain qualitative and quantitative measures of effects on sleep, physiology, and performance at various dose levels; (2) field research, intended to measure drug effects on performance of more "real world" tasks, including, for example, aviator performance in flight simulators or troop performance while on maneuvers; and (3) operational testing, in which selected agents are administered according to preestablished guidelines in an operational environment and the effects observed and monitored by the research team.

Over the past four years, behavioral psychopharmacological research at the Naval Health Research Center (NHRC) has emphasized laboratory evaluation of sleeping aids for operational use. The methodology devised to date in this research program is more generally applicable to the evaluation of all psychoactive drugs, including stimulants, as well as potentially useful in testing the effects of toxic agents and/or antidotes.

## 2. SLEEPING AIDS

The effects of sleep loss on human performance are well-documented. In operational settings, personnel must effectively utilize rest periods which may be brief and irregularly scheduled. Because of the demands of military missions, it may be impossible to schedule sleep periods at biologically suitable times. Or, the nature of the mission may be such that personnel are on edge, aroused, or are

otherwise in a state physiologically incompatible with going to sleep--there may be no biologically suitable times for rest. In such situations, use of a carefully-selected sleeping aid may alleviate situationally-related sleep disturbances.

Elsewhere in these proceedings, some principles of sleep management in operational environments are presented by my colleague from NHRC, Dr. Paul Naitoh. In order to develop a pharmacological sleep management technique, we have evaluated the suitability of various sleeping aids for use in operational settings.

To be suitable for use in operational settings, a sleeping aid must meet specific criteria:

- 1) It must be effective over the period of intended administration in reducing sleep latency and increasing sleep efficiency.
- 2) Adverse effects on performance must be absent or limited to a well-defined time period post-administration; drug-induced alterations in arousability from sleep (such as elevation of auditory arousal threshold) or in memory functions (such as anterograde or retrograde amnesias) must be identified.
- 3) Development of tolerance and occurrence of withdrawal effects and side effects should be rare or nonexistent.

While of substantial clinical value, the sedative-hypnotic flurazepam (Dalmane®) 30 mg was previously found to be inappropriate for operational use because of long-lasting adverse performance effects which persisted through the morning following bedtime administration [3]. More recently, our laboratory research has focused on two potentially suitable sleeping aids, the triazolobenzodiazepine triazolam (Halcion®) and the dietary amino acid, L-tryptophan.

## 2.1 Triazolam

Various members of the class of benzodiazepine drugs are known to be effective hypnotics. Sleep laboratory studies of these agents have focused on measurement of the effects of these drugs on performance, as well as on assessment of their hypnotic efficacy. The triazolobenzodiazepine triazolam was of potential military interest because its short half-life, reported to be within the range of 2-3 hours, suggested that this drug might promote improved nighttime sleep without producing daytime

performance impairment. In earlier studies, triazolam was demonstrated to be an effective hypnotic in doses ranging from 0.25-1.0 mg [4-12]. There had been several previous studies which assessed morning performance following bedtime triazolam administration [5,8,10,13-15]. The results of these studies differed, depending upon the dose size, schedule of performance testing, and type of performance task used. Acute effects of triazolam (0.25 mg and 0.5 mg) on performance were demonstrated at 3.5 hours post-administration in subjects who were awakened from sleep for performance testing [5]. Nicholson and Stone [10] reported that visuo-motor performance was impaired up to 5 hours post-administration of 0.25 mg and 0.5 mg doses in daytime tests of subjects who remained awake.

## 2.2 L-tryptophan

The amino acid l-tryptophan is regularly ingested in the diet as a constituent of protein foods. L-tryptophan has been called a "natural hypnotic" [16,17]. Plasma tryptophan levels, which show a diurnal rhythm with peak levels in the late evening hours, may be a physiological regulator of sleep onset. In earlier sleep laboratory studies, l-tryptophan was reported to significantly reduce sleep latency in doses ranging from 1-15 g [18-24], but not all investigators have found sleep-facilitating effects [16,25-28]. Decreased time awake and/or increased total sleep time were found in some laboratory studies [16,19-21]. In awake subjects, early evening administration of l-tryptophan (2 and 4 g) was demonstrated to increase subjective ratings of sleepiness on the Stanford Sleepiness Scale [29,30]. In our initial evaluation of daytime hypnotic effects, we found that l-tryptophan 4 g reduced nap sleep latency by 46% [31]. Its efficacy in daytime administration suggested its possible operational use in alleviating sleep problems due to jet lag or altered work-rest schedules. There had been little previous research on the effects of tryptophan on performance. Broadhurst [32] found that l-tryptophan 2 g did not slow reaction time in test sessions conducted 2 hours post-administration. Domino and Krause [33] reported that loading doses of tryptophan (32 mg/kg) produced a fairly rapid peak in plasma at 1.2 hours post-administration. Plasma half-life of total tryptophan was 2.7 hours. These pharmacokinetic parameters indicated that any adverse performance effects associated with l-tryptophan administration might be short-lived.

## 3. RESEARCH PROTOCOL

Triazolam 0.5 mg data were collected during the period 1978-1980. L-tryptophan 3 g data were collected during 1980-1982. The procedures for the two studies were identical.

### 3.1 Subjects

Twenty male poor sleepers participated as subjects. To qualify for participation, subjects had to identify themselves as "poor" sleepers, indicate a usual sleep latency of 45 minutes or longer, and report "trouble falling asleep" (i.e., sleep onset insomnia) for at least 6 months. To meet the objective EEG criterion for participation, subjects had to exhibit sleep latencies (time from lights out to the onset of Stage 2 sleep) of 30 minutes or longer in the sleep laboratory on a screening night.

### 3.2 Procedure

A parallel, three-phase design was employed. Subjects who qualified on the screening night went on to complete 11 additional nights of the 12-night protocol (Fig. 1).

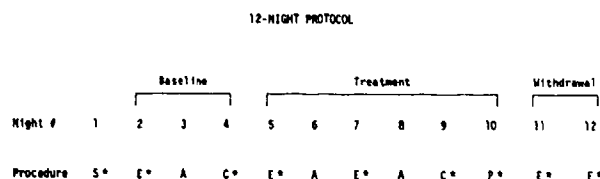


Fig. 1. Protocol for 12-night triazolam and l-tryptophan studies. Procedure code: S=screening night; E=all-night EEG for sleep stage scoring; A=auditory arousal thresholds obtained; C=auditory evoked potentials obtained; P=performance batteries administered during awakenings from sleep; \*=morning performance testing.

Following the screening night, subjects received placebos in a single-blind paradigm for 3 consecutive baseline nights. Following the placebo-baseline nights, 10 subjects received the active agent for 6 nights while the other 10 continued to receive placebo in a double-blind paradigm. After the 6 treatment nights, all subjects received placebo on 2 withdrawal nights. Lights out was at 2200 and subjects were awakened at 0530. All-night sleep EEGs were recorded according to standard laboratory procedures.



### 3.3 Sleep Measures

Sleep latency was scored for all study nights. All-night sleep stage data were obtained for statistical comparisons on nights 2, 5, 7, 11, and 12. Sleep measures were: Total Sleep in minutes (the sum of minutes in Stages 2, 3, 4, and REM); Stage 1 percent (minutes of Stage 1 divided by Total Bedtime x 100); Stage 2 percent, Stage 3 percent, Stage 4 percent, and Stage REM percent (minutes in each stage divided by Total Sleep x 100); Sleep Efficiency (Total Sleep divided by Total Bedtime x 100); Wake Time (minutes awake while in bed); Wake percent (minutes awake divided by Total Bedtime x 100).

### 3.4 Performance Measures

#### 3.4.1 Morning Performance

Performance batteries were administered approximately 20-40 minutes after the morning awakening. Morning batteries included four performance tests: Wilkinson 4-Choice Reaction Time Test, Digit Symbol Substitution Test, Williams Word Memory Test, and Card Sorting Task.

#### 3.4.2 Performance during Awakenings from Sleep

On night 10, subjects were awakened from Stage 2 sleep during three preestablished time windows--90-100 minutes, 180-200 minutes, and 270-300 minutes after lights out--to complete performance tests. Performance testing generally occurred at times 1.5, 3, and 5 hours post-drug ingestion. Following completion of each test battery, the subjects were instructed to go back to sleep. Latency of the return to sleep was recorded.

#### 3.4.3 Memory

The effects of triazolam on retention of material learned prior to drug administration were evaluated through use of a paired associates (P-A) learning task. On study nights 2, 4, 5, 7, 9, 11, and 12, approximately 1 hour prior to drug administration, the subject learned 10 word pairs from a tape-recorded list. Morning P-A testing included recall and matching tasks. To check for anterograde amnesic effects, in the morning following night 10, subjects were presented with the Memory Checklist. This list contained the 90 words which were presented in the Williams Word Memory Task during nighttime test sessions plus 90 filler words. Subjects were instructed to identify the words which had been

presented during the nighttime sessions.

### 3.5 Arousal Threshold Measures

The threshold for arousal from sleep was obtained on 3 recording nights: night 3 (placebo-baseline), night 6 (second treatment night), and night 8 (fourth treatment night). The subject's threshold for tones while awake was obtained prior to lights out. To obtain arousal thresholds, tones were begun at 20 dB above the awake threshold and were incremented in 5 dB steps until the subject made the behavioral (three button pushes) and verbal ("I'm awake") responses. Tones were 2 seconds long and occurred at 16-second intervals. Arousals were performed six times: #1: during the first Stage 2 sleep, 5 minutes after the sleep onset; #2: during the first SWS (Stage 3 or Stage 4), 20 minutes after the return to sleep following the first arousal; #3: in Stage 2, 150-210 minutes after lights out (0030-0130); #4: in Stage 2, 270-330 minutes after lights out (0200-0330); #5: in Stage 2, 370-430 minutes after lights out (0410-0510); #6: the morning arousal, at 0530. After the subject made the appropriate response, he was told to go back to sleep. The dB level for the highest tone presented and the latency (in minutes) from the time of the awakening to the return to sleep were recorded.

## 4. LABORATORY FINDINGS

The major findings regarding hypnotic efficacy and effects on performance and arousal threshold for triazolam and L-tryptophan are described below. Only statistically significant effects are reported.

### 4.1 Triazolam

Triazolam significantly reduced sleep latency, and increased total sleep time and sleep efficiency. Stage 2 percent increased and Stage 4 percent decreased. REM percent was reduced during treatment. REM percent, Stage 2 percent, and Stage 4 percent returned to placebo-baseline levels during withdrawal. Sleep latency returned to placebo-baseline values but did not exceed these values during withdrawal. Consistent with the laboratory data, triazolam subjects reported a significantly reduced subjective estimate of sleep latency during treatment. A plot nighttime of mean sleep latencies is presented in Fig. 2.

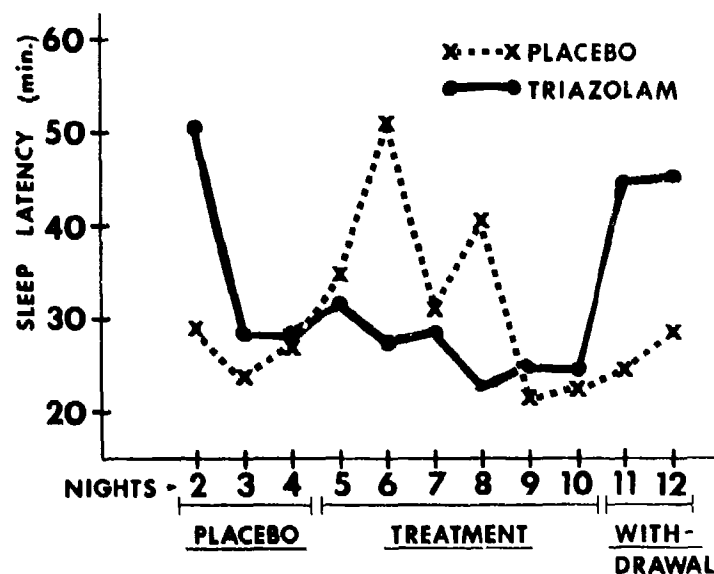


Fig. 2. Triazolam study: mean sleep latency for nights 2-12.

At the time of morning test sessions, approximately 8.25 hours post-administration, there were no significant differences between the placebo and triazolam groups on performance measures. However, in the nighttime testing, triazolam administration was shown to significantly impair performance on each task at 1.5, 3, and 5 hours post-administration. Performance data showed a trend toward recovery at the time of the third nighttime test session, approximately 5 hours post-drug, and full recovery was evident at the time of the morning test session. As an example, Night 10 data for the Wilkinson 4-Choice Reaction Time Task are presented in Fig. 3.

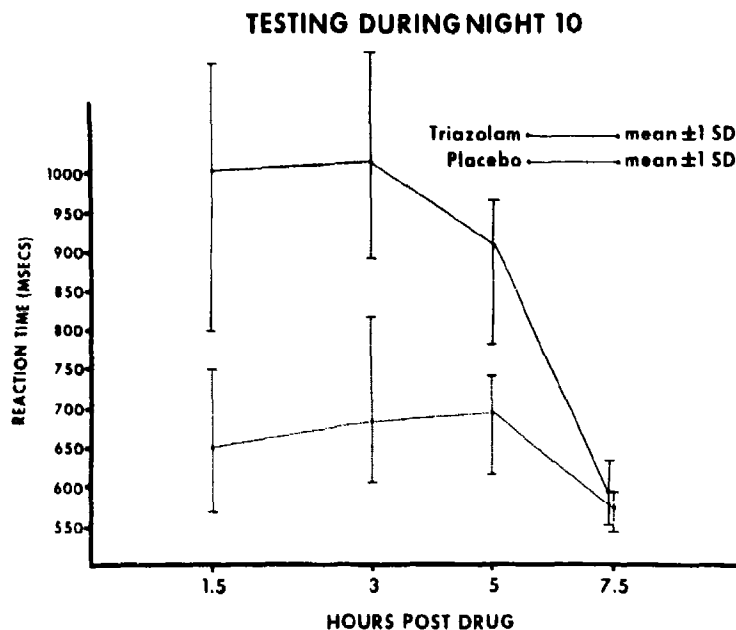


Fig. 3. Triazolam study: mean reaction time on the Wilkinson 4-Choice Reaction Time Task during awakenings from sleep at 1.5, 3, and 5 hours post-drug and in morning testing.

Triazolam subjects also had a significantly lower score (number correct) on the Memory Checklist in the morning following Night 10, indicating that anterograde amnesic effects were produced by triazolam administration. Performance on P-A recall and matching tasks were not altered by triazolam.

Compared to arousal threshold of placebo subjects, threshold for triazolam subjects was significantly higher during treatment at the time of the first, second, and third arousals (Fig. 4). Within the triazolam group, arousal threshold was significantly elevated during SWS. Over time, the placebo subjects appeared to become more sensitive to the tone and had significantly reduced arousal thresholds during the treatment. Latency of return to sleep following arousal by tones was significantly reduced for the first through third arousals in triazolam subjects.

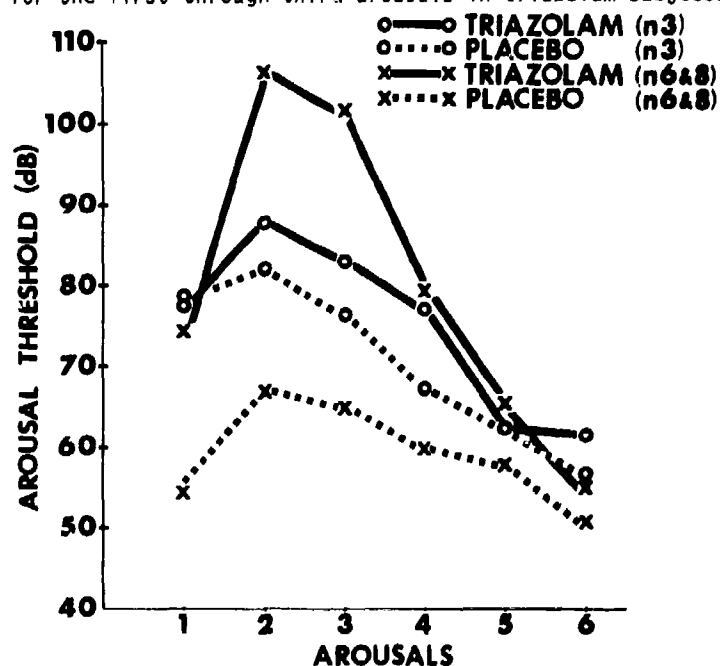


Fig. 4. Triazolam study: mean arousal thresholds for placebo-baseline (n3) and for the mean treatment (n6 & 8).

More detailed reports of our triazolam study have been published in the scientific literature, including triazolam effects on sleep and performance [34], brain electrical activity [35], and heart rate during sleep [36].

#### 4.2 L-Tryptophan

Night-by-night sleep latency data are presented in Fig. 5. L-tryptophan significantly reduced sleep latency on the fourth-sixth treatment nights. No other sleep measures were altered by l-tryptophan administration.

MORNING PERFORMANCE, PERFORMANCE DURING AROUSALS FROM SLEEP, AND AROUSAL THRESHOLD WERE NOT AFFECTED BY TRIAZOLAM. PERFORMANCE ON MEMORY TASKS WAS NOT IMPAIRED DURING L-TRYPTOPHAN ADMINISTRATION.

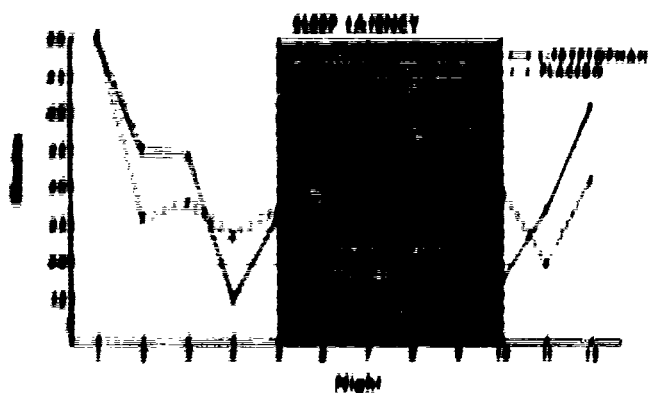


Fig. 5: L-tryptophan study: mean sleep latencies for all study nights.

#### 6. SLEEPING AIDS FOR OPERATIONAL USE: DISCUSSION

Results from our laboratory studies suggest that both triazolam 0.5 mg and L-tryptophan 3 or 4 g may be successfully administered in selected operational settings. After review of detailed data on hypnotic efficacy and time course of effects on performance, pragmatic decisions can be made regarding which hypnotic to select for use, based on consideration of the requirements of the mission and the operational environment.

We found that triazolam was effective as both a sleep-inducing and a sleep-maintaining agent. Morning performance, at 8, 16 hours post-administration, was fully recovered to placebo-baseline levels. However, at 1, 5, 3 and 5 hours post-triazolam, performance on all laboratory tasks was impaired, revealing the acute adverse effects of triazolam on choice reaction time, cognitive processing, and short-term memory. We also found from analysis of the morning Memory Checklist data that triazolam had produced anterograde amnesic effects--impairment of recall for stimuli presented during the effective phase of drug action. Retrograde amnesia was not a correlate of triazolam use, as reflected in intact memory for paired associates, which were learned prior to drug administration. Another important feature of triazolam's stated behavioral effects is the elevation of arousal threshold associated with its use; this alteration of the sleeper's responsiveness to auditory stimuli would act to protect and maintain sleep in noisy environments. However, this effect might also render the sleeper impervious to important auditory signals used in an operational environment. It is suggested that triazolam 0.5 mg

could be administered in situations in which personnel may be scheduled for rest periods of 8 hours duration. Based on our data, up to 5-hours post-administration, personnel would be more difficult to arouse from sleep, would perform less effectively when awake, and would have mnemonic impairment for information presented during this time period.

For l-tryptophan, the absence of performance effects is an important factor in its potential usefulness to the military. However, the hypnotic efficacy of l-tryptophan requires further discussion. In our earlier study assessing its daytime effectiveness [31], substantial sleep-inducing effects were present on the first day of administration. In the 12-night study, hypnotic effects were not evident until the fourth night of administration. There were, in fact, three differences between the two studies: type of subject, dose size (3 versus 4 g), and time of day. All subjects in the nap study reported being "average" or "good" sleepers, while, for the nighttime study, we specifically chose "poor" sleepers who had a persistent sleep onset problem, in order to provide a rigorous test of the efficacy of the sleeping aid. Our results are compatible with the notion that there may be a biochemical correlate of chronic poor sleep which is gradually altered by l-tryptophan treatment. Alternatively, chronic poor sleepers may have a substantially different psychological "set" regarding sleep which is psychologically and, ultimately, psychophysiologicaly incompatible with sleep onset. The late hypnotic effects of l-tryptophan in chronic poor sleepers may reflect the gradual dissolution of the psychological set to stay awake, mediated by repeated experience with the physiological deactivation produced by l-tryptophan administration. It is important to note, of course, that the subjects in the daytime study were theoretically in a physiological state incompatible with sleep onset, since they were asked to nap during their normal daytime working hours. The operationally-relevant question, as yet unanswered, is whether personnel in operational environments will respond to l-tryptophan as normal sleepers trying to rest at odd and unusual times for sleep or as poor sleepers trying to sleep at normal bedtimes.

The issue of the adequacy of the 3 g dose is also of interest. It may be the case that a larger bedtime dose would have promoted sleep onset on the first night of administration in poor sleepers. Schneider-Helmert [37] noted that in three studies of psychiatric patients with severe insomnia [16,17,38], the effective dose range was 4-7.5 g, but the sleep-enhancing effects seen in these patients may have been more related to antidepressant effects of l-tryptophan rather than to primary hypnotic effects. Brown et al. [23] found that l-tryptophan 3 g reduced sleep latency on some but not all nights of administration in laboratory-screened insomniacs. Hartmann et al. [21] have already shown that the dose-response curve for l-tryptophan 1-15 g and sleep is "flat" for normal sleepers, although from Hartmann and Spinweber [24], it is clear that the 1 g is the smallest dose having hypnotic effects

in normal sleepers. There are, thus, no strong data to suggest that a larger dose would have greater hypnotic efficacy, although there is reason to suspect that there may be a smallest effective dose for various subject populations.

Finally, in consideration of the time of day difference between the two studies, we suggest that this factor is the least impressive and is, perhaps, the most counter-intuitive as an explanation for the differences in sleep latency between the two studies. Persons generally should be more ready for sleep at night and, as suggested by Conner [39], tryptophan should be most potent as a hypnotic in the evening, rather than in the daytime, hours. The final resolution of the remaining questions about triazolam and l-tryptophan will be possible after field research and operational testing phases are completed.

## 6. FUTURE DIRECTIONS

To date, we have focused on one side of the psychopharmacological coin in our effort to devise performance enhancing strategies. In our research, we have pursued the identification of sleeping aids suitable for use in operational settings to promote rapid sleep onset and permit efficient utilization of rest periods. However, in certain operational settings, there may be no opportunity for scheduled rest. Therefore, a second performance-enhancing psychopharmacological technique, use of carefully selected stimulants to maintain alertness and performance effectiveness, is required. In the past, amphetamines were used to elevate arousal level, alleviate fatigue, and improve attention. These drugs, while effective, were unreliable in operational settings because of well-described undesirable side effects. However, a host of non-amphetamine stimulants are available, as well as more natural agents, such as peptides and xanthines, which are potentially appropriate for military use. The protocols we have developed in our on-going behavioral psychopharmacology research program will also be employed to develop a second psychopharmacological technique based on use of stimulants.

## REFERENCES

1. Physicians' Desk Reference. Thirty-sixth Edition, New Jersey, Medical Economics Company, Inc., 1982.
2. Goodman, L. S. and Gilman, A. The Pharmacological Basis of Therapeutics. Sixth Edition, New York, Macmillan, 1980.
3. Church, M. W. and Johnson, L. C. Mood and performance of poor sleepers during repeated use of flurazepam. *Psychopharmacology*, 1979, 61: 309-316.
4. Roth, T., Kramer, M., and Schwartz, J. L. Triazolam: a sleep laboratory study of a new benzodiazepine hypnotic. *Curr. Ther. Res.*, 1974, 16: 117-123.
5. Roth, T., Kramer, M., and Lutz, T. The effects of hypnotics on sleep, performance, and subjective state. *Drugs Exp. Clin. Res.*, 1977, 1: 279-286.
6. Roth, T., Kramer, M., and Lutz, T. The effects of triazolam (.25 mg.) on the sleep of insomniac subjects. *Drug Exp. Clin. Res.*, 1977, 1: 271-277.
7. Vogel, G., Thurmond, A., Gibbons, P., Edwards, K., Sloan, K. B., and Sexton, K. The effect of triazolam on the sleep of insomniacs. *Psychopharmacologia (Berlin)*, 1975, 41: 65-69.
8. Vogel, G. W., Barker, K., Gibbons, P., and Thurmond, A. A comparison of the effects of flurazepam 30 mg and triazolam 0.5 mg on the sleep of insomniacs. *Psychopharmacology*, 1976, 47: 81-86.
9. Kales, A., Kales, J. D., Bixler, E. O., Scharf, M. B., and Russek, E. Hypnotic efficacy of triazolam: sleep laboratory evaluation of intermediate-term effectiveness. *J. Clin. Pharmacol.*, 1976, 16: 399-406.
10. Nicholson, A. N. and Stone, B. M. Activity of the hypnotics, flunitrazepam and triazolam, in man. *Br. J. Clin. Pharmacol.*, 1980, 9: 187-194.
11. Ogura, C., Nakazawa, K., Majima, K., Nakamura, K., Ueda, H., Umezawa, Y., and Wardell, W. M. Residual effects of hypnotics: triazolam, flurazepam, and nitrazepam. *Psychopharmacology*, 1980, 68: 61-65.
12. Pegram, V., Hyde, P., and Linton, P. Chronic use of triazolam: the effects on the sleep patterns of insomniacs. *J. Int. Med. Res.*, 1980, 8: 224-231.
13. Veldkamp, W., Straw, R. N., Metzler, C. M., and Demissianos, H. V. Efficacy and residual effect evaluation of a new hypnotic, triazolam. *J. Clin. Pharmacol.*, 1974, 14: 102-111.
14. Roth, T., Hartse, K. M., Saab, P. G., Piccione, P. M., and Kramer, M. The effects of flurazepam, lorazepam, and triazolam on sleep and memory. *Psychopharmacology*, 1980, 70: 231-237.
15. Hindmarch, I. and Clyde, C. A. The effects of triazolam and nitrazepam on sleep quality, morning vigilance, and psychomotor performance. *Arzneim. Forsch./Drug Res.*, 1980, 30(11): 1163-1166.
16. Wyatt, R. J., Engelman, K., Kupfer, D. J., Fram, D. H., Sjoerdsma, A., and Snyder, F. Effects of l-tryptophan (a natural sedative) on human sleep. *Lancet*, 1970, 2: 842-846.
17. Hartmann, E., Chung, R., and Chien, C. P. L-tryptophane and sleep. *Psychopharmacologia (Berlin)*, 1971, 19: 114-127.
18. Hartmann, E. L. The effect of l-tryptophan on the sleep-dream cycle in man. *Psychon. Sci.*, 1967, 8: 479-480.
19. Williams, H. L., Lester, B. K., and Coulter, J. D. Monoamines and the EEG stages of sleep. *Activ. Nerv. Sup. (Praha)*, 1969, 11: 188-192.
20. Griffiths, W. J., Lester, B. K., Coulter, J. D., and Williams, H. L. Tryptophan and sleep in young adults. *Psychophysiology*, 1972, 9: 345-356.
21. Hartmann, E., Cravens, J., and List, S. Hypnotic effects of l-tryptophan. *Arch. gen. Psychiat.*, 1974, 31: 394-397.



22. Hartmann, E. and Elion, R. The insomnia of 'sleeping in a strange place': effects of l-tryptophan. *Psychopharmacology*, 1977, 53: 131-133.
23. Brown, C. C., Horroni, N. J., and Wagman, A. M. I. Effects of l-tryptophan on sleep onset insomniacs. *Waking and Sleeping*, 1979, 3: 101-108.
24. Hartmann, E. and Spinweber, C. L. Sleep induced by l-tryptophan. Effect of dosages within the normal dietary intake. *J. nerv. ment. Dis.*, 1979, 167: 497-499.
25. Brezinova, V., Loudon, J., and Oswald, I. Tryptophan and sleep. *Lancet*, 1972, 2: 1086-1087.
26. Adam, K. and Oswald, I. One gram of l-tryptophan fails to alter the time taken to fall asleep. *Neuropharmacology*, 1979, 18: 1025-1027.
27. Nicholson, A. N. and Stone, B. M. L-tryptophan and sleep in healthy man. *Electroenceph. clin. Neurophysiol.*, 1979, 47: 539-545.
28. Small, J. G., Milstein, V., and Golay, S. L-tryptophan and other agents for sleep EEG. *Clin. Electroenceph.*, 1979, 10: 60-68.
29. Hartmann, E., Spinweber, C. L., and Ware, C. L-tryptophan, l-leucine, and placebo: effects on subjective alertness. *Sleep Res.*, 1976, 5: 57.
30. Spinweber, C. L. Daytime effects of l-tryptophan. *Psychopharmacol. Bull.*, 1981, 17: 81-82.
31. Spinweber, C. L., Ursin, R., Hilbert, R. P., and Hilderbrand, R. L. L-tryptophan: effects on daytime sleep latency and the waking EEG. *Electroenceph. clin. Neurophysiol.*, 1983, in press.
32. Broadhurst, A. D. Tryptophan and sedation. Presented at 2nd Conference of I.S.T.R.Y., University of Wisconsin, Madison, Wisconsin, August 10-12, 1977.
33. Domino, E. F. and Krause, R. R. Plasma tryptophan tolerance curves in drug free normal controls, schizophrenic patients and prisoner volunteers. *J. Psychiat. Res.*, 1974, 10: 247-261.
34. Spinweber, C. L. and Johnson, L. C. Effects of triazolam (0.5 mg) on sleep, performance, memory, and arousal threshold. *Psychopharmacology*, 1982, 76: 5-12.
35. Johnson, L. C. and Spinweber, C. L. Effect of a short-acting benzodiazepine on brain electrical activity during sleep. *Electroenceph. clin. Neurophysiol.*, 1981, 52: 89-97.
36. Muzet, A., Johnson, L. C., and Spinweber, C. L. Benzodiazepine hypnotics increase heart rate during sleep. *Sleep*, 1982, 5: 256-261.
37. Schneider-Helmert, D. Interval therapy with l-tryptophan in severe chronic insomniacs. *Int. Pharmacopsychiat.*, 1981, 16: 162-173.
38. Bergonzi, P., Chiurulla, C., Capocchi, G., Mennumi, G., and Tempesta, E. Sleep patterns of psychiatric patients following l-tryptophan administration. *Electroenceph. clin. Neurophysiol.*, 1976, 41: 321-322.
39. Cooper, A. J. Tryptophan antidepressant 'physiological sedative': fact or fancy? *Psychopharmacology*, 1979, 61: 97-102.

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20. ABSTRACT (continued)

decrement was present up to 5 hours post-administration. Triazolam also produced anterograde amnesia and elevated auditory threshold for arousal from sleep. In operational use, triazolam could be effectively administered when rest periods of 8 hours duration are scheduled. The dietary amino acid l-tryptophan 4 g was effective in reducing daytime sleep latency in normal sleepers, suggesting its usefulness in alleviating sleep disturbances associated with jet lag and altered work-rest schedules. In nighttime administration to chronic poor sleepers, l-tryptophan 3 g reduced sleep latency after three nights of administration and had no adverse performance effects. The suitability of both triazolam and l-tryptophan for military use will be further evaluated in field research and tested in operational environments. Another psychopharmacological approach is administration of carefully-chosen stimulants to maintain alertness and performance effectiveness when there is no opportunity for sleep. The techniques developed in this on-going research program in behavioral psychopharmacology will be employed to evaluate stimulants for operational use.

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